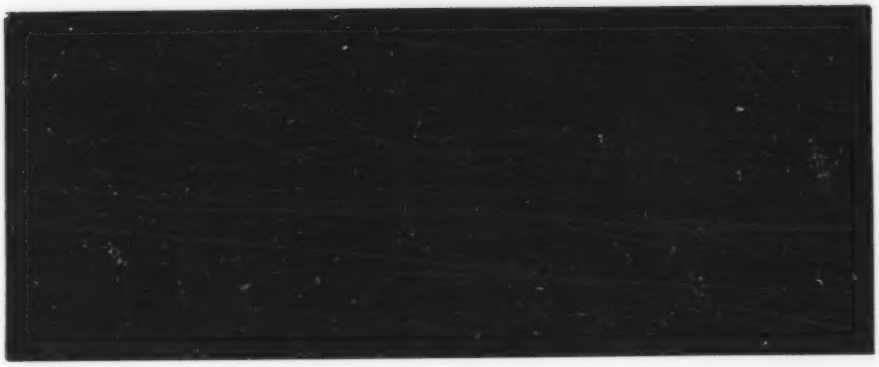
ADF

Saskatchewan
Agriculture
Development Fund

Keeping the agriculture and food industries competitive through Research, Development and Demonstration.



91-05732/

Technical/Final Report
to
Saskatchewan Agriculture Research Fund

Use of Alpa-2 Adrenoreceptor Antagonists to Relieve Ruminal Statis in Ruminal Lactic Acidosis (Grain Overload)

S-86-01-~~0003~~ 0014

SASKATCHEWAN AGRICULTURE
LIBRARY COPY

EXECUTIVE SUMMARY

1. Agricultural Database Abstract

The early loss of forestomach motility in livestock suffering from grain overload leads to further complications in this disease because toxic levels of D-lactic acid are produced from the abnormal fermentation of high energy feeds which stagnate in the rumen. If forestomach motility can be restored or maintained in these animals, the severity of the disease will be greatly diminished and their recovery enhanced. In this study, forestomach motility was restored and maintained by administering drugs which block adrenoreceptors (adrenoceptor antagonists) to 8 sheep with loss of forestomach motility resulting from grain overload. During the period of re-stored forestomach motility animals showed no adverse side effects. The findings of this study not only indicate a successful method of restoring forestomach motility in animals experiencing ruminal lactic acidosis, but more importantly provide a tentative method of treating livestock suffering from grain overload. In view of the clinical implications of these findings, an in-depth evaluation of this method is warranted.

2. Results and Impact on Saskatchewan Agriculture.

Ruminal lactic acidosis (grain overload) is a disease of economic importance to the livestock industry of Saskatchewan since it readily develops in livestock fed high energy feeds, for example dairy cows and feedlot cattle. The loss of forestomach motility which occurs early in the development of this disease is responsible for the severity and subsequent complications which develop, because the high energy feeds which become

stagnant in the rumen are abnormally fermented to produce toxic levels of non-metabolizable D-lactic acid. If forestomach motility can be restored or maintained in ruminal lactic acidosis, the severity of the disease will be drastically reduced and recovery will be greatly enhanced.

In the present study, normal forestomach motility was successfully restored in sheep suffering from ruminal lactic acidosis, for a period of 4 hours, after administration of 2.5 to 5.0 mg/kg of adrenoceptor antagonists. Since treated animals did not show any adverse side effects, this finding not only illustrates a successful method of restoring normal forestomach motility in animals with ruminal lactic acidosis, but also provides a tentative method of treating livestock suffering from grain overload.

The ability to successfully restore forestomach motility in animals experiencing ruminal lactic acid may be of economic importance to livestock producers in Saskatchewan. With the ability to maintain forestomach motility, ingested high energy feeds will not stagnate in the rumen and thus the production of toxic levels of D-lactic acid will be drastically reduced. With a decrease in D-lactic acid levels, normal recovery of afflicted livestock will be greatly enhanced, thereby eliminating financial losses presently incurred by the livestock industry from this disease.

TECHNICAL REPORT

Abstract

Ruminal lactic acidosis was induced in 8 rumen fistulated sheep by placing finely ground wheat into the rumen. Within 8 to 12 hours of the intra-ruminal placement of wheat, forestomach contractions were severely depressed or completely absent. At this time, the administration of adrenoceptor antagonists, within a dosage range of 2.5 to 5.0 mg/kg, induced increases in rate and amplitude of forestomach contractions which persisted for up to 4 hours. An augmentation in heart rate and an increased state of excitement, lasting about 10 minutes, were the only adverse side effects observed with the highest dose of adrenoceptor antagonists. In anesthetized sheep this dose elicited a decrease in mean arterial blood pressure and a reflexive increase in heart rate which lasted for 30 to 40 seconds.

Acidification of the duodenum by lactic acid produced in the rumen has been suggested as the cause of the loss of forestomach motility in ruminal lactic acidosis. In this study, the loss of forestomach motility in sheep experiencing ruminal lactic acidosis was not accompanied by any of the characteristic patterns of duodenal myoelectrical activity which normally accompany duodenal acidification. This finding thus indicates that duodenal acidification may not be the causitive factor for loss of forestomach motility in sheep experiencing ruminal lactic acidosis.

Background and Objectives

Ruminal lactic acidosis is an economically important disease in agriculture, since it readily occurs in ruminant livestock that are

maintained on high energy feeds such as dairy cows and feedlot cattle. The loss of forestomach motility which occurs early in the development of ruminal lactic acidosis is a major contributing factor towards the severity of the disease since ingested feeds which stagnate in the forestomach are abnormally fermented to produce toxic levels of non-metabolizable D-lactic acid. If forestomach motility can be maintained or restored during ruminal lactic acidosis, the severity of the disease will be reduced since feed will not stagnate in the forestomach and, consequentially, recovery will be greatly enhanced.

Loss of forestomach motility in ruminal lactic acidosis results from the activation of forestomach epithelial receptors by nondissociated volatile fatty acids within forestomach contents. Activation of these receptors produce a reflexive inhibition of brainstem neurons which initiate the cyclical contractions of the forestomach. Neural pathways which mediate inhibition of gastrointestinal functions are reported to incorporate adrenoceptors.

Drugs which activate adrenoceptors, for example xylazine, induce inhibition of forestomach contractions in ruminant livestock. Drugs which block these adrenoceptors, for example yohimbine and tolazoline, abolish inhibition of forestomach motility. Although adrenoceptor antagonists are effective in removing inhibition of forestomach motility, their use in re-establishing or maintaining forestomach motility in ruminal lactic acidosis has not been explored. In view of this, the objective of this study was to determine whether adrenoceptor antagonists, such as tolazoline, are capable of re-storing forestomach motility that has been lost in domestic ruminants suffering from ruminal lactic acidosis.

Experimental Methods

Surgical preparation of animals - Eight Suffolk cross bred sheep (40-50 kg) were anesthetized with Somnotol (Sodium pentobarbital, 30 mg/kg, M.T.C. Pharmaceuticals, Mississauga, Canada) and fitted with permanent rumen cannulas to facilitate the intraruminal placement of wheat and the sampling of ruminal contents. Fine nichrome wire recording electrodes (Johnson Matthey Metals Limited, London, England), were implanted in the muscle walls of the reticulum, dorsal and ventral sacs of the rumen and duodenal bulb to record myoelectrical activity generated in these regions. Strain gauges were also sutured to the serosal surfaces of the reticulum and rumen to record the tensions generated by contractions of these forestomach areas. Following a post-surgical recovery period of 3 weeks, animals were individually housed in modified metabolism cages where alfalfa-brome hay, water and a salt block were available at all times. Prior to the induction of ruminal lactic acidosis, hay was removed for 18 hours. Ruminal lactic acidosis was induced by placing finely ground wheat (50 g/kg), combined with an equal volume of water, into the rumen via the rumen cannulas.

Forestomach motility recordings - Recordings of reticular contractions began 8-10 hours before wheat was placed in the rumen, and continously thereafter until the experiment ended. The level of forestomach motility was assessed by the frequencies of reticular myoelectrical discharges and the amplitudes and frequencies of strain gauge recordings generated by reticular and ruminal contractions.

Duodenal myoelectrical activity recordings - To record duodenal myoelectrical activity, the free ends of the duodenal recording wire electrodes were connected to minature electrical connectors which were, in turn, attached to the input amplifiers of a multi-channel Grass polygraph

(Grass Instruments Co., Quincy, Massachusetts, USA). The output from the amplifiers was also fed into an integrator which produced an output of the summed duodenal myoelectrical activity every 20 seconds. This integrated record was used to determine when premature duodenal regular spiking activity (RSA) occurred and to measure the duration of the migrating myoelectric complex (MMC). The duration of an MMC was measured from the end of the RSA of one MMC to the end of the RSA of the subsequent MMC.

Collection of rumen contents and venous blood - Samples of ruminal contents were collected before wheat was placed in the rumen and every 2 hours thereafter. The pH of these samples was determined immediately after the samples were collected and the osmolality was measured (in triplicate) on a Model 5100C vapour pressure osmometer (Wescor Inc., Logan, Utah, USA). The average of these osmolal readings was taken as the osmolality of the sample.

Blood samples were anaerobically obtained, at the time of ruminal fluid collection, from a catheter within the right jugular vein. The pH and partial pressure of CO_2 were measured on a Model 178 Corning pH/blood gas analyzer (Corning Scientific Instruments, Medfield, Massachusetts, USA) immediately after the samples were collected, and the serum bicarbonate concentrations were then calculated from these values.

Experimental procedures - Following the intra-ruminal placement of wheat, the development of ruminal lactic acidosis was assessed by the pH and osmolarity changes in rumen contents, the pH, serum bicarbonate levels, and the base excess status of venous blood, and the levels of forestomach motility. When ruminal stasis developed or severe hypomotility was observed, the animals were treated, intravenously, with the adrenoceptor antagonist, tolazoline, at dosages of 0.2, 0.4, 1.0, 2.5, 4.0 and 5.0

mg/kg. Following treatment, recordings of forestomach contractions and forestomach myoelectrical activity were monitored for signs of recovery of forestomach motility. Recordings of duodenal myoelectrical activity were monitored during the loss of forestomach motility for evidence of patterns of myoelectrical activity associated with duodenal acidification. After drug administration, animals were closely monitored for signs of adverse side effects.

Results and Discussion

Reticulo-ruminal contractions that were lost or severely depressed, in 8 sheep suffering from ruminal lactic acidosis, induced by intra-ruminal loading with finely ground wheat, were restored after administration of 2.5, 4.0 and 5.0 mg/kg of the adrenoceptor antagonist, tolazoline. Significant increases in the rates of reticulo-ruminal contraction became evident within 5 to 8 minutes after drug administration and persisted in 6 sheep up to and beyond the time the wheat was flushed out of the rumen (1 hour after drug administration). In 2 sheep in which the wheat was not removed, forestomach motility was maintained up to 4 hours after a single treatment. In these animals, additional injections were required to maintain forestomach motility at the initially induced levels. After 12 hours of treatment, these animals were able to independently maintain forestomach motility. After forestomach motility was re-established the sheep began to eat and were alert, whereas during ruminal stasis they were anorexic and depressed.

During the re-establishment and maintainance of reticulo-ruminal contractions the pH of the rumen contents ranged from 3.97 to 4.57. In untreated animals, forestomach motility remained severely inhibited at

these pH levels. Shortly after administration of 5.0 mg/kg of the adrenoceptor antagonists, heart rate increased and the animals displayed increased excitement which did not persist beyond 10 minutes. In 2 sheep that were anesthetized, administration of this dose caused a decrease in mean arterial blood pressure from 100 mm Hg to 50 mm Hg and a reflexive increase in heart rate from 96 to 132 beats/minute. These changes were short lived, only lasting 30 to 40 seconds.

Loss of forestomach motility in ruminal lactic acidosis has been suggested to result from acidification of the proximal duodenum by excessive amounts of D-lactic acid produced in the rumen. Recordings of the myoelectrical activity of the proximal duodenum did not show any of the patterns of duodenal myoelectrical activity which normally accompany duodenal acidification, before, during or after the loss of forestomach motility. In view of this finding, it appears that loss of forestomach motility in sheep experiencing ruminal lactic acidosis is not due to proximal duodenal acidification.

Conclusions and Impact

Forestomach motility that was lost or severely diminished in sheep suffering from ruminal lactic acidosis was restored after treatment with drugs which block adrenoreceptors (adrenoreceptor antagonists). This finding not only demonstrates a method of restoring and maintaining forestomach motility in animals with ruminal lactic acidosis, but more importantly indicates a potential treatment of livestock suffering from grain overload.

Publications

Crichlow E.C. (1987) Duodenal Migrating Myoelectric Complex (MMC) in sheep during induced ruminal lactic acidosis. Proceedings of the Conference of Research Workers in Animal Disease 68:10 (Abstract #56).

Statement of Expenditures

Statements of expenditures for period ending October 31, 1988

Salaries	$13,973
Fringe Benefits	651
Materials and Supplies	2,331
Travel	358
Equipment	170
Equipment Maintenance	42
Feed	477
Total	$18,002
Revenues received	$16,200
Balance	$ 1,802

Personnel involved in project

May 1, 1987 to August 31, 1987	
Ramon E. Crichlow	100%
John J. Cruickshank	33%
Rodney C. Gale	66%
October 1, 1987 to May 31, 1988	
Christian Falkenberg-Andersen	30%